

LV function
ESPR
Diastolic function

Are Contraction and Relaxation Coupled in Patients With and Without Congestive Heart Failure?

Eric J. Eichhorn, MD; John E. Willard, MD; Luis Alvarez, MD; Anatole S. Kim, MD;
D. Brent Glamann, MD; Richard C. Risser, MS; and Paul A. Grayburn, MD

Background. Although changes in contractility are often accompanied by changes in relaxation, a mathematical model of ventricular coupling has not been described. A model we examined suggests a hyperbolic relation between measurements of contraction and relaxation. We thus tested the hypothesis that relatively load-independent measurements of contractility (end-systolic elastance [Ees]) and relaxation (the slope of the τ -to-end-systolic pressure relation [R]) were coupled.

Methods and Results. To establish the validity of the model, an assessment of Ees and R was made in 30 subjects who underwent sequential digital ventriculography and micromanometer pressure measurements during atrial pacing ($93 \pm 10 \text{ min}^{-1}$) before and after graded doses of nitroprusside. To establish if a cyclic AMP (cAMP)-mediated intervention alters coupling, seven of the 30 subjects were studied before and after 3 months of β -blockade. To determine if a non-cAMP-mediated intervention alters coupling, 12 other patients were studied before and after deslanoside. Nonlinear regression analysis for the initial 30 patients suggested a hyperbolic relation: $(\text{Ees})(\text{R}) = 1.05$ ($r = 0.79$, $p < 0.001$) with an inflection point near $\text{Ees} = 1.02 \text{ mm Hg/ml}$. Thus, with normal or near-normal contractility, relaxation is normal and not load dependent (R is close to 0). With systolic dysfunction, relaxation becomes very afterload dependent and so must be normalized for load. After long-term β -blockade in patients with severe left ventricular dysfunction, small improvements in contractility (elastance) occurred with larger changes in relaxation, but the curve describing the relation was not displaced. Acute administration of deslanoside resulted in a large increase in elastance and a smaller change in relaxation but did not alter coupling. However, the magnitude of the change in R was dependent on the predrug R value.

Conclusions. These data suggest contraction and relaxation may be physiologically coupled with relaxation relatively preserved in early heart failure and more rapid deterioration in relaxation as elastance falls under 1.02 mm Hg/ml . Both β -blockers (which may act through cAMP) and digitalis (which is cAMP independent) improve contraction and relaxation, but both mechanisms appear to maintain coupling. The hyperbolic relation between contraction and relaxation may have important implications regarding therapeutic response and selection of patients for clinical trials in heart failure. (*Circulation* 1992;85:2132-2139)

KEY WORDS • contraction • relaxation • heart failure • digitalis • β -adrenergic blockade

Previous investigators have suggested that relaxation is controlled by three factors: load, inactivation, and nonuniform distribution of load and inactivation in space and in time.¹⁻⁷ Although several investigators have observed either in vitro⁸⁻¹³ or in vivo¹⁴⁻¹⁶ changes in relaxation occurring concomitantly with changes in contractility (induced by either β -agonist or Ca^{+2} therapy), a firm relation between changes in

contractility and alterations in relaxation has not been defined. We hypothesized that the inotropic and lusitropic states of a heart are coupled such that a change in one might predict a change in the other. The most likely reasons to suspect this is true are that 1) both contraction and relaxation are modulated primarily by sarcolemmal and sarcoplasmic calcium flux and cyclic AMP (cAMP) (which is in turn modulated by β -adrenergic, vasoactive intestinal peptide, histamine, adenosine, and muscurinic pathways)¹⁷ and 2) increased contractility can result in heightened systolic deformation of elastic structures with creation of more prediastolic potential energy that may be released during isovolumic relaxation.^{1,14} As the former plays a dominant role in determining relaxation rates¹ and as congestive heart failure is associated with defects in both the β -adrenergic-adenylate cyclase system¹⁸ and intracellular calcium handling,¹⁹ we postulated that changes in inotropic state in normal hearts might not result in the same changes in relaxation as in dysfunctional hearts.

From the Cardiac Catheterization Laboratory and Department of Internal Medicine (Division of Cardiology), Dallas Veterans Administration Hospital and University of Texas Southwestern Medical Center, Dallas, Tex.

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Address for reprints: Eric J. Eichhorn, MD, Director, Cardiac Catheterization Laboratory (IIA2), University of Texas Southwestern and Dallas Veterans Administration Medical Centers, 4500 S. Lancaster, Dallas, TX 75216.

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Because of these common pathways that are known to modulate intracellular events and the previous observations of altered contraction and relaxation to inotropic stimulation, we attempted to develop a physiological construct of the contraction-relaxation relation. We hypothesized that contraction and relaxation are coupled events, and we reasoned that changes in adrenergic tone (which regulates calcium flux via cAMP) may alter coupling in a different fashion from digitalis preparations (which regulate calcium flux via Na,K-ATPase).

Methods

Theoretical Considerations

As contraction and relaxation are load-dependent events, we attempted to eliminate this variable by evaluating a mathematical model to relate these two states to each other using two relatively load-independent indexes. End-systolic elastance (Ees) is a relatively load-independent measurement of contractility.²⁰⁻²² However, to assess relaxation in a relatively load-independent fashion, we measured isovolumic relaxation (τ

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or T) at multiple afterloads. The slope of the τ -to-end-systolic pressure (Pes) relation (R) is a relatively load-independent measure of relaxation as τ is reasonably preload independent.⁵ Thus, with load accounted for, the major determinants of changes in relaxation were inactivation and nonuniform distribution of load and inactivation in space and in time. To minimize changes in relaxation due to nonuniformity of load and inactivation, we did not examine patients with left ventricular aneurysms.

Mathematical Model

Mathematical definition of elastance proposes that Ees can be related to Pes and end-systolic volume (Ves) by the following relation²⁰⁻²²:

$$Pes = Ees (Ves - V_0) \quad (1)$$

The relation of τ to Pes can be expressed by the following^{4,6}:

$$\tau = R (Pes) + T_0 \quad (2)$$

where T_0 is the relaxation time at zero pressure (extrapolated intercept), and R is the slope of the Pes-to- τ relation. Equation 2 can be rearranged to solve for Pes:

$$\tau - T_0 / R = Pes \quad (3)$$

By substituting this equation for Pes in Equation 1:

$$(\tau - T_0) / R = Ees (Ves - V_0) \quad (4)$$

Rearranging this equation yields:

$$(Ees)(R) = k \quad (5)$$

where $k = (\tau - T_0) / (Ves - V_0)$. Equation 5 suggests a hyperbolic relation may exist between R and Ees. That is to say, a relatively load-independent measure of contractility can be related to a relatively load-independent measure of relaxation by a hyperbolic relation.

Patient Selection

To evaluate this model in humans, 42 male patients ranging in age from 33 to 75 years (54 ± 12 years, mean \pm SD) and who had varying degrees of left ventricular function were studied in the cardiac catheterization laboratory at the Dallas Veterans Administration Medical Center, Dallas, Tex. Initial validation of the mathematical model was performed in 30 patients, each of whom underwent one assessment of left ventricular function. To determine the effect of a cAMP-dependent intervention on ventricular coupling, seven of these patients were studied twice, both before and after long-term therapy with the β -adrenergic blocker bucindolol. The overall hemodynamic results from these patients have been previously reported.²³ No patient was chosen who had a large dyskinetic or an aneurysmal regional wall motion abnormality or evidence of primary valvular heart disease. To determine the effect of a cAMP-independent intervention on ventricular coupling, 12 other patients with heart failure underwent assessment of Ees and R before and immediately after acute infusion of a rapid digitalis preparation, deslanoside. Written informed consent was obtained from each patient, and the protocol was approved by the Human Studies Subcommittee of the Dallas Veterans Administration and University of Texas Southwestern Medical Centers in December 1987.

Hemodynamic Study

Using a femoral approach, an 8F double-chip Millar (Millar Instruments, Houston, Tex.) micromanometer pigtail catheter was positioned in the left ventricle such that one transducer recorded left ventricular pressure while the other transducer recorded simultaneous aortic pressure. This catheter contains a central lumen that allows performance of a left ventriculogram while simultaneous micromanometer pressures are recorded. In addition, a 6F bipolar pacemaker was placed in the right atrium.

Atrial pacing was initiated at 15 min^{-1} above the intrinsic heart rate and maintained throughout the protocol. Baseline left heart pressure recordings were performed including aortic and left ventricular pressures. Recording was made on an optical strip-chart recorder (Honeywell Electronics for Medicine model VR-16) at 100 mm/sec paper speed.

The time constant of exponential isovolumic pressure fall, τ was determined using a program developed at the University of Arizona.^{7,24} The micromanometer analog signal from the strip-chart recorder was interfaced with an IBM AT computer equipped with an analog-digital converter. Approximately 50 beats of the pressure signal was digitized on-line and stored at 200 Hz. The digitized study was subsequently recalled for analysis, and a 5-point moving average smoothing routine was applied. Thus, each cardiac cycle was digitized at a rate of roughly 150–200 points per cardiac cycle, depending on the cycle length. The program automatically identifies end-systole, end-diastole, peak positive, and peak negative dP/dt for each beat of the acquisition. The decay of left ventricular pressure with time can be closely approximated by the exponential relation²⁴:

$$P = P_0 e^{-at} + P_B$$

where P is left ventricular pressure, P_0 is the difference between P and P_B at time zero (at peak negative dP/dt), t is the time in msec after peak negative dP/dt , P_B is left ventricular asymptote pressure (assuming a nonzero asymptote and assuming that left ventricular pressure decays to infinity), and a is the constant of the exponential relation. The first derivative of this equation with respect to t is the following:

$$dP/dt = -aP_0e^{-at}$$

If one then substitutes P from the first equation to eliminate P_0e^{-at} :

$$dP/dt = -a(P - P_B)$$

Thus, τ was calculated using a linear regression of dP/dt versus $(P - P_B)$ from maximum negative dP/dt to left ventricular end-diastolic pressure ($\tau = -1/a$ [the inverse of the slope of the regression]). Beats with an r value (correlation coefficient) of less than 0.95 for this linear regression were discarded, and 20–30 beats were analyzed and averaged. No patient was discarded for lack of 20 beats with an r value greater than 0.95. This method was chosen to measure τ , as the method of Weiss et al²⁵ makes the nonphysiological assumption that left ventricular pressure falls monoexponentially toward zero pressure.²⁶

Hemodynamic measurements were followed by digital ventriculography using 15–25 ml (total volume) of diluted (60:40) nonionic contrast media (Iohexol, Winthrop-Breon Laboratories, New York). Ventriculography was performed at 30 frames per second with cineradiographic equipment (Philips model Optimus M200, Eindhoven, The Netherlands) interfaced directly to a digital radiographic computer (ADAC, model DPS-4100C, Milpitas, Calif.) and stored as a $512 \times 512 \times 8$ -bit image matrix. An R wave-gated mask was derived from the cardiac cycle before the appearance of radiographic contrast and subtracted from the respective frames containing contrast. During digital ventriculography, simultaneous left ventricular pressures were acquired and stored by the ADAC computer. Left ventriculography was performed in a 30° right anterior oblique projection. Before the first ventriculogram, a standardized grid at the mid left atrial level was imaged at the same focal length and image intensifier height as the ventriculograms.

After these measurements were recorded, loading conditions were altered while maintaining atrial pacing. Intravenous sodium nitroprusside was initiated at a dose of 0.25–0.50 $\mu\text{g/kg/min}$ and increased by 0.25 $\mu\text{g/kg/min}$ every 2–5 minutes to achieve a reduction of 10–20 mm Hg in aortic Pes. Care was used to avoid symptomatic hypotension. Repeat hemodynamics and ventriculography were performed at one (two patients) or two (28 patients) time points after aortic Pes had been altered. There was a delay of at least 10 minutes between ventriculograms to allow the left ventricle to return to equilibrium.

For the seven patients who returned after 3 months of β -adrenergic blocker therapy, the same procedure was used with care to match the original atrially paced heart rate used in the baseline study.

Hemodynamic Protocol for the Group Receiving Digitalis

The effect of deslanoside on the coupling relation was evaluated in an additional 12 patients by using a slightly

different protocol. Atrial pacing was again maintained throughout the study at 15 min^{-1} above baseline rate. Hemodynamics were measured at baseline, followed by left ventriculography as previously detailed. One dose of nitroprusside was administered (instead of two), and measurements were repeated. The nitroprusside was then discontinued, and pressure was allowed to return to baseline. Deslanoside (0.8 mg; Sandoz Pharmaceuticals Corp., East Hanover, N.J.) was administered intravenously followed by a 30-minute waiting period for onset of action. This was followed by repeat hemodynamics and left ventriculography both before and after repeat nitroprusside administration.

Data Analysis

Left ventricular volumes were measured by analysis of digital left ventriculography. The cardiac cycle selected was not a premature beat or postpremature beat. Analysis of the cardiac cycle was performed by computer gating of the RR interval into 33-msec segments. Each cardiac image in the cycle underwent light-pen digitization by a blinded observer. Left ventricular volumes, including end-diastolic, end-systolic, and stroke volumes, were determined by a standard angiographic area-length method.^{27,28} End diastole applied to the largest ventricular volume (near the peak of the R wave) and end systole was taken as the smallest volume in each cardiac cycle and usually corresponded with the left upper corner of the pressure-volume loop. Simultaneous left ventricular pressure recordings were interfaced directly onto the digital volume assessment at each data point in the cardiac cycle. The ADAC digital computer plotted simultaneous pressure and volume for all data points in the cardiac cycle.

Intraobserver and interobserver variabilities of our digital ventriculogram measurements were tested by repeated analysis of 21 digital left ventricular volumes. The SEE for intraobserver measurements was 4.5 ml ($n=21$, $r=0.99$, $y=0.86x+25.8$, $p=0.0001$), and the SEE for interobserver measurements was 4.8 ml ($n=21$, $r=0.99$, $y=0.97x-3.7$, $p=0.0001$).

A regression analysis of the Pes volume points was made for each patient. The slope of this relation was the Ees. A regression analysis of the τ -to-Pes relation was also determined with the slope designated as R.

Statistics

Based on the mathematical model of a hyperbolic relation, nonlinear regression models were fit to the data. An ANCOVA approach was used to evaluate the significance of an additive displacement in the coupling constant (k) between groups of patients or patients treated under different conditions. To determine the independent significance of changes in Ees or R after an intervention (either β -blockade or deslanoside), a paired Student's t test was used. Results of statistical tests were considered significant when the observed probability value was less than 0.05. Results are expressed as mean \pm 1 SD.

Results

As can be seen in Figure 1, the relation of τ to Pes is linear. In these three representative patients with varying left ventricular function, there were strong correla-

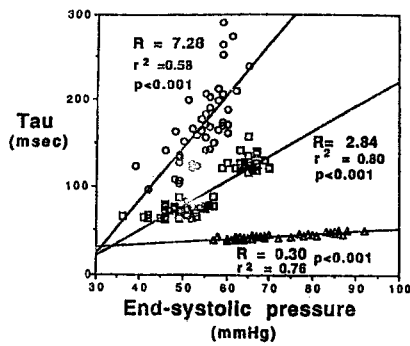


FIGURE 1. The linearity of the relation of isovolumic relaxation time (τ) as a function of the covariate end-systolic pressure is demonstrated for three patients. The slope of this relation represents the load dependency of isovolumic relaxation, R . As is evident, τ is afterload dependent with little differences between patients at low end-systolic pressures. At higher end-systolic pressures, larger differences in τ can occur. Thus, R is a more load-independent measurement of relaxation.

tions between τ and P_{es} . Thus, our use of the slope of this relation (R) as a reflection of relaxation (or the load dependence of τ) is justified. As R increases, the afterload dependence of τ increases. It is clear from Figure 1 that just reporting isovolumic relaxation times as a measure of relaxation is inadequate in patients with increased R values, as τ is afterload (and heart rate) dependent. However, as τ is relatively insensitive to preload,^{4,5} R represents a relatively load-independent measurement of isovolumic relaxation (assuming constant heart rate).

A plot of the data relating E_{es} to R for our initial validation studies in 30 subjects can be seen in Figure 2. As is evident, there was a hyperbolic relation between E_{es} and the slope of the τ -to- P_{es} relation ($r=0.79$, $p<0.001$). The equation that best fits this relation is:

$$(E_{es})(R)=1.05$$

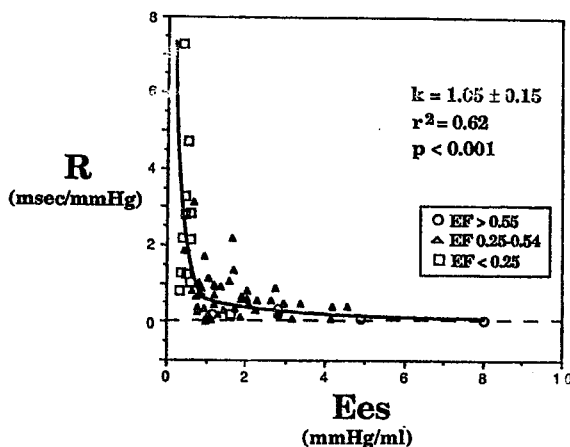


FIGURE 2. The relation of the load dependency of isovolumic relaxation (R) as a function of end-systolic elastance (E_{es}) is depicted. As the mathematical model suggests, this relation is hyperbolic. Thus, for severe heart failure and E_{es} values below the inflection point of 1.02 mm Hg/ml, small improvements in contractility may result in larger improvements in relaxation (R), assuming constant coupling.

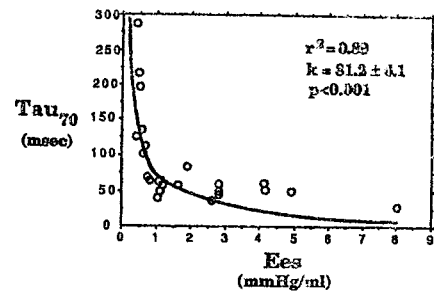


FIGURE 3. Isovolumic relaxation rate normalized to an end-systolic pressure of 70 mm Hg (τ_{70}) as a function of end-systolic elastance (E_{es}) is shown. A hyperbolic relation is maintained, suggesting that lusitropy worsens precipitously only after significant systolic dysfunction is present.

The inflection point of the curve occurs at an E_{es} of 1.02 mm Hg/ml. Thus, with normal or near-normal contractility, relaxation is normal and not load dependent (i.e., R is close to 0). However, as contractility worsens, R is relatively preserved (i.e., R is close to 0) until significant systolic dysfunction is present. Relaxation and the afterload dependence of relaxation then worsen at a rapid rate for any further deterioration in systolic function.

Afterload Dependence of Relaxation Versus Normalized Relaxation Rate

As R is a reflection of the afterload dependence of the relaxation rate (τ), we examined if the actual relaxation rate normalized for P_{es} was likewise influenced in a hyperbolic fashion by E_{es} . To do this, we arbitrarily examined τ at a P_{es} of 70 mm Hg (τ_{70}) and compared this with E_{es} (Figure 3). As is evident in Figure 3, a hyperbolic relation was maintained. This is not unexpected based on Equation 2 of our theoretical considerations as τ at any P_{es} will be a function of R . This suggests that R not only reflects afterload dependence of the relaxation rate but also reflects the actual relaxation rate corrected for afterload. Thus, it is a relatively load-independent measurement of relaxation. We further compared τ_{70} with the load-dependent measure of contractility, left ventricular ejection fraction (Figure 4). This relation demonstrates a sharp decline in lusitropy below an ejection fraction of 0.30 in most cases.

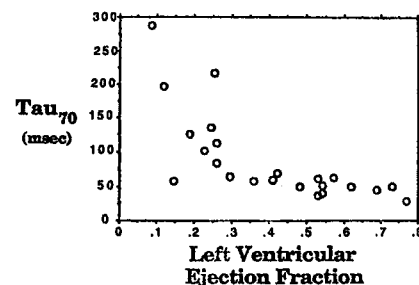


FIGURE 4. Isovolumic relaxation rate normalized to an end-systolic pressure of 70 mm Hg (τ_{70}) as a function of left ventricular ejection fraction is shown. Below an ejection fraction of 0.30, lusitropy declines rapidly in most cases.

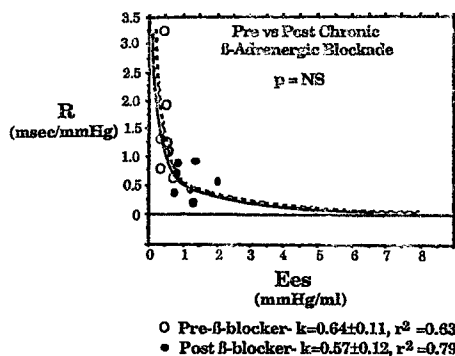


FIGURE 5. The effect of chronic β -blockade in heart failure is depicted in this graph. \circ , Patients on digitalis before β -blockade; \bullet , same patients after β -blockade. ---, Patients before β -blockers; —, same patients after β -blockade. As β -blockade improves both relaxation and contractility yet does so without shifting to a new curve, coupling is maintained.

Effect of Long-term β -Adrenergic Blockade on Coupling

Long-term treatment with β -adrenergic blockers was assessed in seven patients with severe heart failure. This therapy resulted in an improvement in contractility (i.e., an increase in elastance) and relaxation (i.e., a reduction in load dependence of isovolumic relaxation). In these patients, Ees increased from 0.47 ± 0.14 to 1.13 ± 0.44 mm Hg/ml after 3 months of β -blockade ($p=0.008$), whereas R decreased from 1.45 ± 0.89 to 0.59 ± 0.27 msec/mm Hg ($p=0.03$). As elastance increased and R decreased, this resulted in a shift in both Ees and R along the curve $(Ees)(R)=0.64$ (Figure 5). As is evident, long-term β -blocker therapy resulted in a shift down the same curve rather than a shift to a new curve ($p=NS$ versus before β -blockers). Thus, the relation of contraction to relaxation is unchanged with chronic β -blocker therapy.

Acute Intervention With Deslanoside

Because the above comparisons were chronic studies, we wanted to examine the acute effect of deslanoside, a fast-acting digitalis compound, on this relation. We found an increase in elastance from 1.59 ± 0.81 to 2.15 ± 0.99 mm Hg/ml ($p<0.01$) and a decrease in R from 0.83 ± 0.60 to 0.54 ± 0.42 msec/mm Hg ($p<0.05$). As can be seen in Figure 6, this results in no shift in coupling (from $k=0.90 \pm 0.23$ to 0.86 ± 0.22 , $p=NS$). After deslanoside, τ did not change at baseline loading conditions (from 72 ± 12 to 76 ± 16 msec, $p=0.16$) as Pes increased (from 74 ± 17 to 83 ± 18 mm Hg, $p<0.005$). Thus, the improvement in myocardial relaxation may have been masked without correction for load. In addition, as is evident from Figure 7, the baseline value for R influenced the change in R after intervention. As the relation of Ees to R is hyperbolic, at low Ees values (high R values), the curve is most steep. Thus, the most marked changes in R can be seen for any change in Ees.

Discussion

These data suggest that contraction and relaxation may be coupled but not in a linear fashion. As heart failure progresses and contractility worsens, relaxation is relatively well preserved until severe systolic dysfunction is present (the inflection point of the hyperbola).

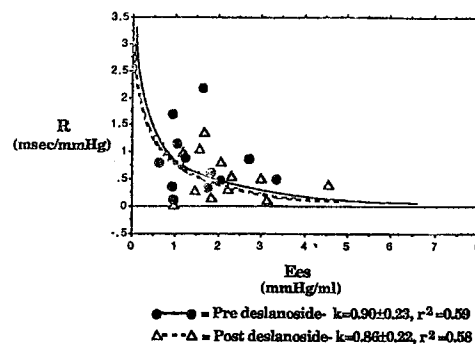


FIGURE 6. The effect of the acute administration of deslanoside on coupling is depicted in this graph. Although both contractility and relaxation improved with the administration of deslanoside, coupling did not change.

The hyperbolic relation between Ees and R suggests that relaxation worsens more rapidly as ventricular systolic function declines below the inflection point. This is especially true below the inflection point of the curve, which for grouped data from this study is at an elastance of 1.02 mm Hg/ml. Thus, in patients with severe congestive heart failure, small improvements in contractility may result in large lusitropic improvements. This is exemplified by the deslanoside data, where patients with the largest baseline R value (i.e., the sickest hearts with Ees values below the inflection point) showed the most marked improvement in relaxation with digitalis. This may explain why some heart failure patients exhibit marked symptomatic improvement (improved relaxation) despite only mild improvement in contractility. These data also suggest that ventricles with the worst systolic function have the poorest relaxation and the most load-dependent relaxation. Thus, their diastolic properties may be enhanced both by improving their systolic performance and by lowering left ventricular systolic pressure. Furthermore, these findings suggest that the selection of heart failure patients for a clinical trial may influence the hemodynamic outcome, especially if isovolumic relaxation is being examined. For example, had we examined only patients with mild heart failure and relatively large Ees values, we may have missed any effect on relaxation despite measurable changes in contractility. Detecting

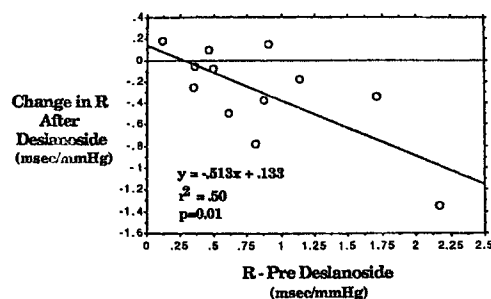


FIGURE 7. For the 12 patients receiving deslanoside, the change in the load dependency of isovolumic relaxation (R) is graphed as a function of the baseline R value. As is evident, the sicker hearts with larger R values showed the most improvement in R while less sick hearts failed to show much improvement in this parameter.

an effect on isovolumic relaxation may be masked even more if τ is not normalized for afterload. This is exemplified by a lack of effect on τ seen in the patients given deslanoside as P_{es} increased. Heart failure patients have low P_{es} values (despite high wall stress) leading to small differences in τ despite larger differences in R (Figure 1). This may explain why other investigators have not found an effect of digitalis on myocardial relaxation. However, in patients with normal or near-normal contractility, R approaches 0, and τ does not need to be corrected for load as relaxation is relatively load independent. Based on Figure 4, we would recommend correction of τ for afterload in any patient with an ejection fraction less than 0.30.

Previous Investigation Into Physiological Coupling

Previous investigators who have tried to examine changes in contraction-relaxation coupling have observed variable coupling relations. Parmley and Sonnenblick⁹ found a decrease in the time required for tension to fall to one half its peak value in cat papillary muscle after isoproterenol, but for an equal increase in developed tension, calcium increased relaxation time. Karliner et al²⁹ had similar findings in conscious dogs, although calcium decreased (not increased) isovolumic relaxation time. These data suggest that isoproterenol may acutely shift the relation down the hyperbolic curve in a similar fashion as long-term β -blockade. However, calcium infusion may shift the entire hyperbola upward. Cohn and coworkers⁸ found that isoproterenol or calcium infusions in anesthetized dogs increased peak positive dP/dt disproportionately to peak negative dP/dt , whereas Grassi de Gende et al¹² and Mattiazzi et al¹¹ reported the opposite effect of isoproterenol (i.e., contractility affected less than relaxation). These data are not inconsistent with our findings that moderately healthy or healthy hearts (i.e., hearts with elastance values of 0.8–3.0 mm Hg/ml) may be on the flat portion of the hyperbola such that a large increase in contractility may be accompanied by only small changes in isovolumic relaxation times. This is exemplified by a hypothetical patient with an E_{es} of 1.5 mm Hg/ml, a τ of 20–40 msec, and a peak negative dP/dt of 1,500 mm Hg/sec. Relaxation times and peak negative dP/dt cannot improve much beyond this, whereas E_{es} may increase significantly. On the other hand, severely failing hearts may have large changes in relaxation with smaller changes in contractility.

Skomedal et al¹⁰ found that α -adrenergic stimulation increases isometric contraction and relaxation equally, whereas β -agonists effected larger changes in relaxation compared with contraction. These data suggest that α -agonists may not shift the hyperbola, although species differences prevent firm conclusions.^{11,18}

Parker and Colucci³⁰ found a markedly attenuated inotropic response (measured by a percentage change in peak $+dP/dt$) to intracoronary dobutamine in heart failure compared with normal hearts. This finding may result from β -receptor subsensitivity in congestive heart failure.³¹ These investigators also found a greater decrease in isovolumic relaxation times in the heart failure group compared with patients with normal hearts. This would have been especially true had they corrected isovolumic relaxation times for an increase in systolic

pressure seen only in the heart failure patients. Our data agree with these findings. Assuming constant coupling between E_{es} and R , patients with congestive heart failure who have impaired relaxation at baseline and are on the ascending limb of the hyperbola would be expected to have larger lusitropic improvements with smaller inotropic changes when cAMP is increased with a β -agonist.

Little and coworkers¹⁶ found improvements in maximal elastance (E_{max}) and a reduction in τ with the β -agonist dobutamine in canine hearts. However, similar to our results in humans, they found improvements in E_{max} with ouabain without a change in τ . Although Little et al did not correct the measurements of τ for loading conditions or relate contraction and relaxation in a relatively load-independent fashion, the ventricles studied were normal, thus not requiring load correction. However, Little et al may have not seen an effect of digitalis on relaxation because the ventricles studied were normal (with a low R value). As seen in Figure 7, in ventricles with low baseline R values, R changes little with digitalis. Little et al's study in animals and our study in humans suggest that agents that act through β -receptors and cAMP (either dobutamine acutely or β -blockers chronically) alter both contraction and relaxation. In addition, our study demonstrated that the amount of alteration in contractility and relaxation was dependent on the degree of left ventricular dysfunction present during the baseline state (i.e., before intervention).

Possible Mechanisms for These Phenomena

It is unclear why lusitropy is well preserved until significant systolic dysfunction appears. As both contractility and relaxation are controlled by calcium flux within the myocyte, one possible mechanism may be alterations in intracellular calcium handling. It has been well documented that intracellular calcium transients are markedly prolonged in congestive heart failure.^{32–37} One might speculate that calcium "overload" due to the inability of sarcoplasmic reticulum to take up cytosolic calcium does not occur until significant impairment of contractility occurs, at which point relaxation is affected. Although this hypothesis is attractive, a relation of altered calcium transients to functional changes in myocardial contractility and relaxation has not been established. In contrast, other factors besides calcium overload, such as interstitial fibrosis, ventricular hypertrophy, and conduction delays, may increase R rapidly at low elastance values.

The mechanism by which β -blockers improve contractility and relaxation are currently unclear.^{23,38} Speculation has included β -receptor upregulation, changes in the guanine nucleotide-binding regulatory proteins (G proteins), and/or improvement in myocardial energetics.^{23,38} Although any or all of these mechanisms may improve intracellular calcium flux, this has yet to be proven.

By contrast, digitalis preparations act through inhibition of the Na,K -ATPase, leading to an increase in intracellular sodium and ultimately promoting increased intracellular calcium via the Na^+-Ca^{2+} exchanger.³⁹ This promotes enhanced contractility. However, the mechanism by which digitalis preparations enhance relaxation is unknown.

Study Limitations

The greatest limitation of this study was the inability *in vivo* to attempt multiple interventions in each patient to define each patient's coupling constant. Obviously, logistical limitations of a human study preclude such intensive definition of this relation. It is likely that each subject has his or her own coupling relation as defined by this study. That is, the value for k may differ from patient to patient. In this study, we showed group values as we lacked the ability to alter contractility and loading conditions multiple times in humans and were limited by the amount of contrast we could use. Further studies either with a conductance catheter in humans or a study in animals are warranted to demonstrate that this relation exists for each ventricle.

Our mathematical model assumed systolic elastance to be linear.²⁰⁻²² However, more recent investigation has suggested a nonlinear model of elastance, especially at very large or very small elastance values.⁴⁰⁻⁴² As this relation may be nonlinear, the slope of the P_{es} -to-volume relation becomes dependent on the loading range, with elastance being inversely proportional to ventricular size. Despite this limitation, elastance, which we used as a general approximation of contractile state, will still reflect this when measured over a physiological range.⁴⁰ Although several attempts have been made to normalize elastance for ventricular volume^{43,44} and mass,⁴⁴ such attempts have been met with controversy as to an ideal method. Thus, we did not normalize elastance for chamber size. However, we recognize that normalization of elastance might alter the relation between E_{es} and R .

In addition, we took end systole to be end ejection. Although maximal elastance, in theory, occurs at the instant of the maximum left ventricular pressure-volume relation, in the absence of valvular heart disease the temporal relation between end systole and end ejection is very close.^{45,46}

Because patients with congestive heart failure have dilated left ventricles with altered geometry, the geometric assumption of a prolate spheroid for single-plane ventriculography²⁸ may result in some error of volume measurement. This may be especially true in the present study as we used nitroprusside to alter loading conditions. Nitroprusside may result in some geometrical alterations as ventricular volumes decrease and could introduce an error into the volume calculations. Although we produced three pressure-volume loops for 28 of 30 patients who did not receive deslanoside, we only produced two pressure-volume loops for the 12 patients who received deslanoside. The reason for the latter was the dye limitation of four ventriculograms (two pressure-volume loops before deslanoside and two loops after deslanoside) in patients undergoing concomitant coronary angiography. Thus, the error in absolute E_{es} measurement will be greatest in the deslanoside patients. However, as these patients were compared with themselves using nitroprusside before and after deslanoside and as these ventricles were large, the error of calculation resulting from geometric alterations should be of minimal significance. The use of nitroprusside may also result in some baroreflex-mediated changes in contractility.⁴⁵ However, as patients with congestive heart failure have high neurosympathetic tone at baseline,^{45,47} baroreflex stimulation from nitroprusside should

be of minimal significance. In addition, no patient overdrove their atrial pacemaker, suggesting minimal reflex.

Using a previously validated²⁴ method of measuring τ , we chose to measure isovolumic relaxation from peak $-dP/dt$ ($t=0$) to a pressure equal to left ventricular end-diastolic pressure of the following beat. Although some conventions are to measure this regression from peak $-dP/dt$ to 5 or 10 mm Hg above end-diastolic pressure to avoid problems with the mitral valve opening, we feel that this had minimal effect on our results as we chose to use only beats with a regression r value of ≥ 0.95 . Had mitral opening affected dP/dt versus ($P-P_B$), the relation would not have remained linear.

The algebraic derivation for our mathematical model proposed that $(E_{es})(R)=k$ where $k=(\tau-T_0)/(V_{es}-V_0)$. We were concerned whether we could assume that k was constant, as all four of these terms (τ , T_0 , V_{es} , and V_0) are variables. However, theoretically, as elastance increases, $(V_{es}-V_0)$ decreases at a constant P_{es} . If an increase in elastance indeed produces a decrease in R , then $(\tau-T_0)$ will decrease at a constant P_{es} . Thus, the ratio of $(\tau-T_0)$ to $(V_{es}-V_0)$ may stay constant. However, as this was not guaranteed, we performed the clinical investigation to validate or disprove this hypothesis. As Figure 2 demonstrates, the assumption is probably valid. Although some data scatter exists in Figure 2, the relation between E_{es} and R is probably hyperbolic as the fit is reasonably strong ($r=0.79$, $r^2=0.62$, $p<0.001$). The scatter may represent either grouped data (with slightly different k values for each patient) or errors in measurement. Further studies in single ventricles are warranted to determine if $(\tau-T_0)/(V_{es}-V_0)$ is constant.

Finally, as this mathematical model is asymptotic along the x and y axes, the greatest differences between curves will be near the inflection point of the curves. Thus, differences between curves may be masked by points along two different curves that are not near the inflection point yet are closely aligned to each other. We attempted to find patients who had moderate-to-severe left ventricular dysfunction whose E_{es} and R values would be close to the inflection points of the curve(s). Thus, we attempted to maximize any differences that we saw between curves.

Conclusions

In conclusion, left ventricular contraction and relaxation may be coupled in humans. According to our mathematical model, a hyperbolic relation may exist between R , a relatively load-independent measure of relaxation, and E_{es} , a relatively load-independent measure of contractility. This model suggests that myocardial relaxation is relatively preserved until significant left ventricular systolic dysfunction is present. In addition, chronic β -blockade (a cAMP-dependent mechanism) or acute administration of deslanoside (a cAMP-independent mechanism) appears to improve both contraction and relaxation along the hyperbolic curve and does not appear to alter coupling. These findings have important clinical implications regarding therapeutic response in heart failure and selection of patients for clinical trials.

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